International Journal of Microbial Science, ISSN (online) 2582-967X, Volume 3, Issue 1, September 2022, pp. 33-41
Available online at https://internationaljournalofmicrobialscience.com/

Commentary

Tinospora cordifolia as A Potential Anti-HIV Herb

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Article Info

Article history:
Received: December 15, 2021
Accepted: September 15, 2022
Published: September 22, 2022

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Virus "a piece of bad news wrapped in a protein coat" has been defined by Peter Medawar [1]. They are non-cellular organisms, enclosed in a between them is the presence of Reverse-transcriptase and Integrase enzyme systems in RNA virus i.e Retroviruses [3]. RNA viruses generally have very high mutation rates compared to DNA viruses, because viral RNA polymerases lack proof-reading ability of DNA polymerases [4].

Genetic diversity of RNA viruses is one reason why it is difficult to make effective vaccines against them [5]. Humans have been battling viruses since before species had been evolved into its modern forms. For one disease, smallpox we've been able to eradicate it, ridding the world of new cases. However, we have to go through a long way from winning the fight against viruses. Difficulty in the synthetic drug treatment has led to be focused on the source given by a nature (from plants). Among all, one of the deadliest diseases is Acquired Immune Deficiency Syndrome (AIDS). In this review, the potential of *Tinospora cordifolia* as an anti-HIV herb and its therapeutic applications have been analyzed with its future perspectives.

Acquired Immune Deficiency Syndrome (AIDS) was first recognized as a new disease in 1981 [7]. Initially, AIDS was called Gay-related immune deficiency (GRID). In 1982, it was first termed as AIDS by Centre for Disease Control and Prevention (CDC). It was thought that the causative agent of AIDS was lymphadenopathy-Associated virus (LAV) in 1983 [9]. Later, in 1984, authors found that the causative agent of AIDS is HTLV-3 which will be officially called as HIV as declared by International Committee on Taxonomy of Viruses (ICTV) [10]. HIV is classified into: HIV-1 and HIV-2. It has been suspected that HIV-1 and HIV-2 are of Chimpanzee and Sooty mangabeys origin, respectively [7].

HIV belongs to family of Retroviridae of genus Lentivirus [11]. Morphological studies have revealed that it is a small size spherical virus having a diameter of ~120nm [12]. The important feature of Retroviridae family is its genome. HIV contains a positive sense single-stranded RNA (ss-RNA) [11]. The genome size of HIV virus is ~9.8 kb. HIV

genome consists of nine genes in total which are flanked by long terminal repeats (LTRs) on either side of genome [13]. These nine genes of HIV produce 15 different viral proteins. These 15 different proteins are divided into 3 categories: 1)Structural proteins Gal, Pol and Env 2) Regulatory proteins-Tat and Rev 3) Accessory proteins-Nef, Vif, Vpr, and Vpu act [14].

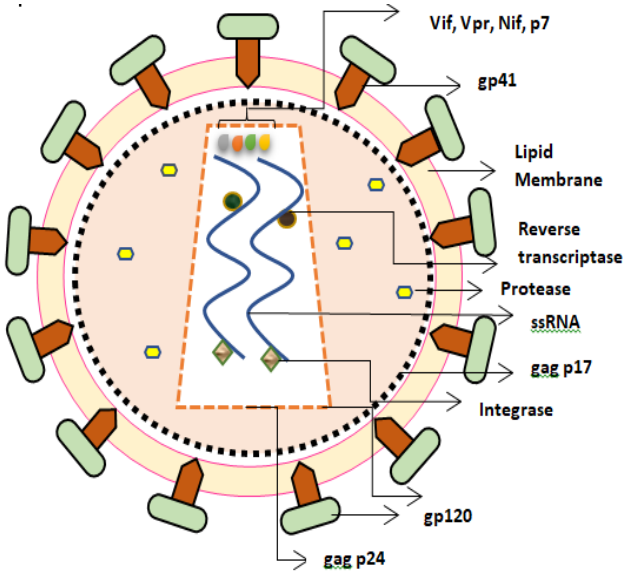

Figure 1: Representation of Human Immunodeficiency Virus showing the outer most layer: lipid membrane; glycoproteins: gp120 and gp120; viral enzymes: Reverse transcriptase, Protease and Integrase; two single stranded RNA; gag protein: gag p24 and gag p17; regulatory proteins: Vif, Vpr, Nif and p7. **Adopted from Kaur et al. 2020 [6] and modified by Shirsat Hrutuja 2022**

Initially, interaction of viral gp120 and host CD4 cells lead to the primary infection of HIV [15]. This can be the first target site for drug development. Patient-derived gp120-reactive antibodies have HIV neutralizing capacity [16]. Peptides derived from gp41 sequences have shown to possess potent antiviral activity [17]. Fusion step can also be an effective target for development of anti-HIV drug [18]. Next step is the conversion of viral RNA into DNA (proviral DNA) which is accomplished by viral enzyme called reverse transcriptase[19]. This gives the drug developer second target site for drug development. Two classes of anti-viral drug exist; nucleoside and non-nucleoside. RT inhibitors inhibit DNA polymerization and are the core component of HAART [20]. Once the proviral DNA is synthesized, it must integrate with the host DNA. The process of integration occurs due to presence of viral *enzyme* called as integrase [21]. This can be the third target site. After that, transcription and translation of proviral DNA occurs with the help of host transcription factor. Tat and Rev are two proteins that support viral replication [22]. After that viral Protease enzyme completes the maturation and release of new infective virions [23]. This can also act as good target to stop viral replication.

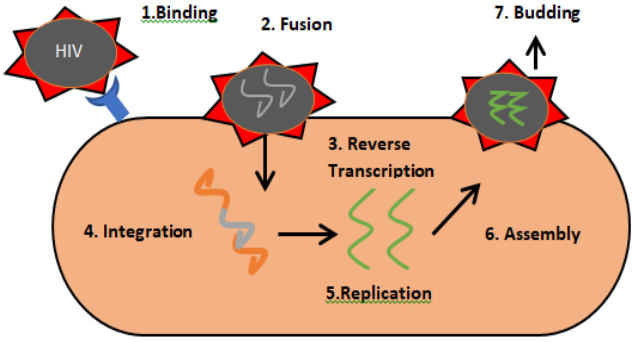

Figure 2: HIV Replication: HIV replication is a series of seven steps; 1: Binding- Viral gp120 gets attached to host CD4 cell. 2: Fusion- Fusion allows virus to enter CD4 cell, where it releases its reverse transcriptase and integrase enzyme.3: Reverse transcription- Conversion of viral RNA to DNA. 4: Integration- Integrates viral DNA into host cell DNA. 5: Replication- Virus uses host machinery to generate viral proteins. 6: Assembly- Newly formed HIV RNA and protein gather to form immature HIV. 7: Budding- Immature HIV is converted into mature HIV virus. **Adopted from Engelman et al. 2012 [8] and modified by Shirsat Hrutuja, 2022.**

Knowledge about the process of viral replication has helped in the development of different group of medications like, Nucleoside reverse transcriptase inhibitors (NRTI), Non- nucleotide reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), integrase inhibitors (IN) [24]. Various antiretroviral drug have also been developed and some are under investigation like fusion inhibitors. The current used strategy for the

treatment of HIV infection is Highly Active Anti-retroviral Therapy (HAART) [25][26]. Beside its efficiency, it has high cost value and most of the people are not able to tolerate the therapy. HIV was found to be resistance to two or more agents in different antiretroviral classes [27], [28]. There is no vaccine and number of side effects of currently used strategy. Therefore, there is need for discovery of novel therapeutic strategies. One of the strategies has been to identify anti-HIV compounds from natural sources, particularly plant.

Traditional medicine has served as a source of alternative medicine, new pharmaceuticals and healthcare products [29]. Medicinal plant science is one of the leading researches globally. Usually plants serve as natural source for drug development as they possess medicinal property and numerous bioactive compounds [30]. Difficulty in drug development arises due to low efficiency, cytotoxicity and development of viral resistance against tested drug [31]. Another antiviral treatment, vaccination, can be applied but they are still under development, as they often provide incomplete protection against virus and their reliability needs more research [32]. Nature has provided another, more reliable source of antiviral agent; plants phytochemicals; almost 40% of currently available drugs are direct or indirect derivatives of plants [33].

Genus *Tinospora* belongs to the family Menispremaceae possessing 32 species. Out of this, *Tinospora cordifolia* is the most medicinally and commercially important [34]. *Tinospora cordifolia* prefers wide range of soil, acid to alkaline and it needs moderate level of soil moisture [35]. It is widely distributed throughout tropical Africa, Madagascar, Australia, Pacific island, Sri-lanka, China, Himalayas, and tropical region of India. It is distributed throughout tropical Indian subcontinent and china, ascending to an altitude of 300m [36].

It is commonly called Guduchi (Marathi), Giloy (hindi), Amritha (Sanskrit), Rasakinda (Sinhala) [37]. In Hindi, the plant is commonly known as Giloe, which is a Hindu mythiological term that refers to the heavenly elixir that has saved celestial beings from old age and kept them eternally young [38]. The term amrita is attributed to its ability to impart youthfullness, vitality and longevity. Guduchi, the Sanskrit name, means one which protects the entire body [39], [40], [41].

Tinospora cordifolia is a large, glabrous, deciduous, climbing shrub with several elongated twining branches [42]. Leaves are simple, alternate, estipulate, long petioles up to 15cm long, roundish, pulvinate, both at the base and apex with the basal one longer and twisted partially and half around. They are membranous and cordate in shape [43]. Lamina broadly ovate or ovate cordate, 10-20 cm long or 8-15 cm broad, 7 nerved and deeply cordate at base, membranous, pubescent above, whitish tomentose with prominent recticulum beneath. The stem are fibrous and transverse section exhibits a yellowish wood with radially arranged wedge shaped wood bundles containing large vessels, separated by narrow medullary rays. It appears in varying thickness, ranging from 0.6-5cm in diameter [35]. The bark is creamy white to gray, deeply left spirally the space in between being spotted with large rosette-like lenticles [44]. Flowers are unisexual. Male flowers are clustered, female usually solitary [35]. Sepals 6, free in two series of three each, outer ones are smaller than the inner. Petals 6 free smaller then sepals, obovate and membranous. Fruits aggregate of 1-3, ovoid smooth drupelets on thick stalk with sub terminal style scars, scarlet or orange coloured [45].

Tinospora cordifolia is categorized as “Rasayana” in Ayurveda [34]. Rasayana, Sanskrit word meaning “path of essence”[46]. According to **Drugs and Cosmetic act of India (1940)**, Giloy is considered as an ayurvedic drug [11]. The stem of

Tinospora cordifolia is approved by Ayurvedic Pharmacopoeia of India [34].

Table 1: Ayurvedic Properties *(dravya-guna)* of *Tinospora cordifolia* (Guduchi) [9]

Rasa	Guna	Virya	Vipaka	Prabhava
Tikta, Kasaya	Laghu, Guru, Snigdha	Ushna	Madhura	Vishaghna

Rasa: Taste; sweet, sour, salt, bitter, pungent and astringent.
Guna: Ten pairs of opposite or mirror image attributes.
Virya: potency.
Ushna: hot, sheeta- cold.
Vipaka: Intestinal digestion and tissue metabolism.
Madhura: neutral, amlaacidic, katu- alkaline.
Prabhava: Specific action through specialized receptors.

Various phytoconstituents have been isolated from *Tinospora cordifolia*, belonging to different classes such as alkaloids, diterpenoids lactones, glycosides, steroids, sesquiterpeniod, phenolics, aliphatic compounds, and polysaccharides. Leaves of the plant are rich in protein (11.2%), calcium and phosphorus.

The whole plant is reported to possess pharmacological activity: antioxidant activity [47-50], antimicrobial activity [51-53], anti-diabetic property [54,55], anti-stress activity [56], hypolipidemic effect [57,58], hepatic disorder [59,60], anticancer activity [61-65], anti-HIV potential [66], wound healing [67-70], anti-osteoporotic effects[71], anti-inflammatory [72,73], anti-arthritic [74], anti-allergic [75], radio protective activity [76], anti-pyretic [77], and immunomodulating activity [78-80]. It is reported that *T. cordifolia* is highly attractive against Parkinosonism [81].

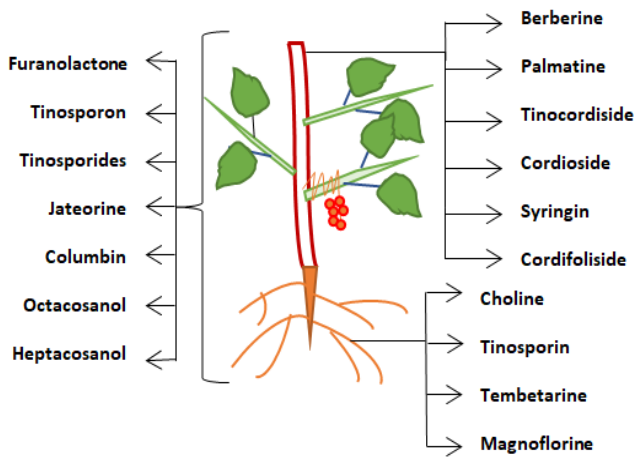

Figure 3: Active principles from alkaloids, glycosides, steroids, aliphatic compound phytoconstituents from different parts of *Tinospora cordifolia* [35]. **Adopted from Bhalerao A.S. et al. 2016 [35] and modified by Shirsat Hrutuja 2022.**

Pharmacognostical and Phytochemical screening of *Tinospora cordifolia* has revealed that the moisture content is 2.31%, total ash was found to be 7.5%, percentage of water and alcohol soluble extract (B-A × 4 ×100/W) was 12.05% and 7.27%, respectively. Nature of extract of stem part was found to be sticky [82-87].

Tinospora cordifolia has been evaluated for its anti-HIV activity. Toxicity test was performed using peripheral mononuclear blood cells (PBMCs) isolated from whole blood. *Tinospora cordifolia* revealed moderate cytotoxic activities against PBMCs with CC50 values ranging from 5.7-12.0 ug/ml. HIV-1 RT inhibition activity was performed using commercial kit. Ethyl acetate extract shows 85% of HIV-1 RT inhibition activity at a concentration of 20 mg/ml [88]. In one of the study on medicinal plants which included *Tinospora cordifolia*, HIV-1 Reverse Transcriptase enzyme inhibition was determined using HIV-RT inhibition assay. To determine whether extract could interfere with binding of CD4 to gp120, Gp120 Binding Inhibition Assay was performed. In order to investigate the mechanism of inhibition of gp120/cd4 binding, a study was conducted to evaluate the time-course effect by adding each

extract before and after binding of gp120 to CD4.It was performed using gp120 Capture ELISA kit (ImmunoDiagnostics,Inc.,USA) [89]. *Tinospora cordifolia* showed significant HIV-RT inhibitory activity. *Tinospora cordifolia* showed highest inhibition of gp120/CD4 interaction by displacing the pre-adsorbed gp120. *Tinospora cordifolia* also inhibited this interaction by binding to immobilized CD4 [89-91].

The importance of natural products for medicine and health is huge. Man's existence has been made possible because of the role of natural products on this earth. The outstanding phenomenon of nature always stands as golden mark for successfully achieving the herbal drug discovery. Every plant is identified by its own unique therapeutic properties. The food and agriculture organization estimated in 2002 that over 50,000 medicinal plants are used across the world [92]. Natural products are a proven source of novel anti-HIV compounds and discovery of promising bioactive molecules involves collaborative work of microbiologist, medicinal, and synthetic chemist, pharmacologists and toxicologist.

Zebrafish (Danio rerio) has been used as a reliable model for infectious diseases and studying the immune function in response to the introduction of human viruses. One of the studies have demonstrated use of Gulvel Ghanvati to reduce the tissue damage caused by SARS-CoV-2-spike protein. Here they have used humanized Zebrafish model [93]. *In-silico* investigation using molecular dyanamic approach can be used to investigate exactly which constituents inhibit the biological activity. In one of the studies, with use of network pharmacology and molecular docking tool, authors were able to conclude that Berberine from *Tinospora cordifolia* can regulate $3CL^{pro}$ proteins function [94]. Computational approach has been used to investigate potential of *Tinospora cordifolia* COVID-19. Pharmacokinetic properties were predicted using pkCSM/ADMET which employs graph based signature to develop predictive models [96].

Nanotechnology is a promising field for its use in drug delivery system. Based on this, scientist had used *Tinospora cordifolia* loaded poly (D, L-lactide) (PLA) nanoparticles (NPs) to evaluate for anti-hyperglycemic potency towards diabetic wistar rat [95].

Tinospora Cordifolia till date has been displayed to inhibit the HIV-protease and HIV-reverse transcriptase activity. With the anti-HIV activity, it has also added immunomodulatory activity, which can be advantageous to HIV-AIDS patient. Drug discovery using natural product is a challenging task for designing new leads. Research in drug discovery needs to develop robust and viable lead molecules, which steps forward from a screening hit to a drug candidate through structural elucidation and structure identification through Gas chromatography-Mass spectrometry (GC-MS), Nuclear Magnetic Resonance (NMR), Infrared Spectroscopy (IR), High Performance Liquid Chromatography (HPLC),and High Performance thin-layer chromatography (HPTLC). With the development of new technology, we can screen new molecules using software and database to establish natural products as a major source for drug discovery. Further target compound from our extract can be separated and identified using preparative High Performance Liquid Chromatography (HPLC), Thin-Layer chromatography (TLC), Radial Chromatography. Preparative HPLC gives best result as we get the compound separately in collecting tube at the end of the procedure. Comparatively HPLC is extremely quick and efficient.

Modern research shows giloy is a strong immune-stimulant and immune-booster builder and has potentially important role in building immune system which in turn can help prevent occurrence of diseases- common cold, diabetes cancer. *Tinospora* has its unique ability to work at

cellular level and enhance immunity and has earned exalted.

Since ancient times, people have used plants for their healing, preventive, curative, rejuvenative and immunomodulating properties. This knowledge has gained global acceptance. Use of active compounds of *Tinospora cordifolia* to enhance the phygocytic ability of macrophages and increase the antibody production by B-cells have been well documented by several workers. Several plants are reported to have immune boosting property. *In-vivo* study will help in evaluating the safety, toxicity and efficacy of our target compound. Structure activity relationship (SAR) studies can help us to find the relationship between the chemical structure of a molecule and its biological activity QSAR –Quantitative Structure Activity Relationship is a statistical method for building statistically computational models. Cell based assay can be done which provides information about toxicity, effect on biological pathway.

Literature survey across different disciplines of study reveals that *Tinospora cordifolia* has been explored in area of biological activity. It exerts anti-HIV activity via multiple mechanism of action. Pharmacological data for *Tinospora cordifolia* support its use in herbal drugs and formulation. Extraction of important biologically active phytochemicals from this plant will certainly be helping in protecting and treating various viral infection and human diseases. So, *Tinospora* would be expected to show inhibitory activity against HIV infection. In order to assess the usefulness of these drugs, more research is needed. Current review summarizes anti-HIV activities of *Tinospora cordifolia* having different target sites, which can lead us towards the development of anti-HIV compound.

Authors' Contributions:

HS: Developed an idea, wrote the manuscript and verified the content.

Competing Interest:

Author declares that no competing interest exists.

Ethical Statement: Since this is a review work, no ethical permission required.

Grant Support Details: This work didn't receive funding from any agency.

Acknowledgement: Author is thankful to Rajesh Dhakane, Assistant Professor, Department of Microbiology, Jayawantrao Sawant Commerce and Science, Hadapsar, Pune, Maharashtra, India for his guidance to publish this commentary.

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Cite this article as: Shirsat HS. Tinospora cordifolia as A Potential Anti-HIV Herb. Int. J. Micro. Sci. 2022;3(1):33-41.